

COLUMBIA'S NOBEL LAUREATES

Scientific breakthroughs, like family traditions, are passed on from generation to generation. One scientist's discovery becomes the foundation for a young upstart's revolutionary hypothesis. Joshua Lederberg, president of Rockefeller University since 1977, made his breakthrough nearly forty years ago when, in his early twenties, he proved a "sexual" stage in bacterial genetic recombination. He received the Nobel Prize in 1958 at the age of thirty-three. His work was made possible, he says, by those who came before him, particularly Francis J. Ryan, the zoology teacher who nurtured the budding young scientist.

Seventeen-year-old Joshua Lederberg crashed into Ryan's life in 1942. "Crashed" is not a hyperbole, according to Elizabeth, Ryan's widow. "You could tell that Joshua was in the lab because you could hear the tinkle of breaking glass. He was so young, bursting with potential over which he had no control. His mind was far ahead of his hands. He frequently broke whatever he was working with."

As an undergraduate in Ryan's laboratory at Columbia, Lederberg read Oswald T. Avery's work-in-progress on DNA. Avery, a Columbia-trained physician working at what was then called the Rockefeller Institute, had confirmed the existence of DNA in 1943, but his scientific paper fell short of claiming that the double helix was the carrier of genetic information. The young student, however, read the paper with "excruciating" pleasure and immediately began with Ryan a series of experiments that eventually culminated in Lederberg's prize-winning work.

Ryan had come to Columbia in 1933 intending to take a premedical course. Instead, he completed the doctoral program in zoology in 1941. An athletic man who enjoyed life, Ryan was a superb teacher and researcher who, says Lederberg, "was even wonderful to his dishwasher and secretary."

Ryan and a fellow zoology student, Elizabeth Wilkinson, were married in 1940, and he took a postdoctoral year at Stanford. There he worked with

AN ACHE TO LEARN

Joshua Lederberg

*A brash young
scientist moved from
breaking beakers
to breaking barriers
in genetic recom-
bination.*

BY ESTELLE GILSON

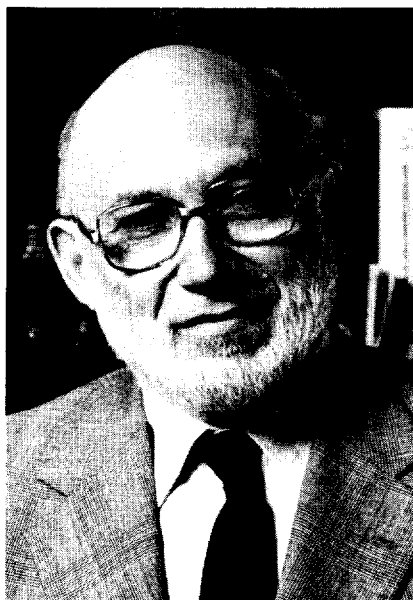
geneticists George Beadle and Edward Tatum who had just begun using *Neurospora*, a reddish bread mold, instead of fruit flies for their genetic studies. Unlike fruit flies and mice, the *Neurospora* could reproduce themselves within days. Somewhat courageously, Ryan brought this botanical substance back to Columbia's zoology department when he returned, a committed molecular geneticist, in the fall of 1942. (Columbia's botany and zoology departments were not combined into the Department of Biological Sciences until 1966.)

Before scientists knew of DNA, they studied inherited characteristics through natural history: first, through botany as in Gregor Mendel's nineteenth-century study of the hybridization of peas; later, through zoology and the study of mammals (primarily mice) and the fruit fly, *Drosophila*. Thomas Hunt Morgan, who taught at Columbia from 1904 to 1928 and conducted ground-breaking *Drosophila* research, received the Nobel Prize in 1934 for having discovered the function of the chromosome in heredity. Morgan brought zoology to the threshold of modern molecular biology; now it was up to a new generation of scientists, including Ryan, to ask and answer questions that the natural scientists had not yet conceived.

"The minute I entered Columbia," Lederberg recalls, "I was knocking on professors' doors, eager to learn." What Lederberg says he found at Columbia, besides "a vast collection of scientific talent" willing to help, was a zoology department "ignited" by news of DNA. Lederberg cannot date his first interest in science. "It was in my earliest consciousness," he says, remembering that as a youngster he "ached to know someone who was a scientist." But his father, Zvi Hirsch Lederberg, was an Orthodox rabbi. Not only was he unable to guide his son, but the two had to reconcile what Lederberg calls his father's "sacerdotal interest and what I was headed for." Eventually they did. "We resolved that we were both looking for truth in our own way. The older I get," he said, "the more I realize the kind of encouragement he gave me. We

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INGBERT GRÜTTNER



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had a lot of respect for each other."

Also guiding Lederberg were scientists whom he calls "family culture heroes"—Albert Einstein and Chaim Weizmann. And there were books, like P. H. de Kruif's *Microbe Hunters*. "By the time I was seven or eight, I was reading everything in sight on science I could lay my hands on. It was random. Whatever I could grab onto that I could also understand."

Joshua Lederberg was born in 1925 in Montclair, New Jersey, the eldest of three brothers. His parents, both of whom were of old Palestinian families, had emigrated to the United States in 1924. Six months after Joshua's birth the family moved to Washington Heights in New York City. In recounting his childhood, Lederberg, like so many of his generation—children of immigrants, whose parents had little or no command of English, and living close to poverty—passes over his early physical deprivation. Clothes, food, toys—he doesn't seem to remember wanting them. But books! Finding books! Seizing them, snatching, grabbing, dragging them home from the shelves of the public library. In a recent presidential report to Rockefeller University, Lederberg spoke of "the heroic accomplishments of European medical science symbolized by *Microbe Hunters*." Memory never closes over some of the books of childhood.

Lederberg graduated from Stuyvesant High School in January 1941. His yearbook notes that he planned to go to City College, but he received a scholarship from Columbia College. He spent the spring and summer before entering college puttering around a laboratory funded by the American Institute of Science, a precursor of the Westinghouse Science Talent Search. Among his labmates were future physicist and Columbia professor Robert Jastrow and virologist and Nobel Prize winner Baruch Blumberg.

At Columbia, says Lederberg, Francis Ryan "took me seriously and he disciplined me; no one else had been able to do that before. I was a very precocious youngster. I had learned that I could outsmart others, and that kind of raw callowness could have gotten me into

very deep trouble. I profited enormously by the discipline he imposed." In the laboratory Lederberg washed Ryan's dishes and boiled his agar. "I'd gladly have washed his floors," he says. While performing these tasks Lederberg learned the fundamentals of scientific research. "My adolescent thinking was sharpened against one of the most versatile, generous minds I would ever encounter."

Columbia also gave Lederberg freedom. As a sophomore he was taking mostly graduate courses. "I'd get an occasional squeak that I really ought to finish my humanities. In a funny way I really wasn't mature enough, and it was just as well that I deferred them until I caught up with that part of my development. But a lot of what happened to me was orchestrated by Ryan. He covered for me in many ways. Although I'm sure it was not as easy as I'm putting out," he laughs.

It wasn't. Lederberg was not easy to get along with, says Elizabeth Ryan. Years later he asked her if he had been lovable, at least. "Not really," she answered. But she remembers his saying that Ryan was like a father to him—even though the teacher was only nine years older than his brash student.

Until 1943, when Lederberg was admitted to the Naval Training Program at Columbia, he lived at home and commuted to the campus. Then he spent a year at St. Alban's Hospital, where one of his duties was examining blood and stool specimens for parasites. "I had a chance to see parasites at first hand and in great volume, in a way that not many are privileged to do now. And I believe that looking at the life cycle of these microbial parasites had a lot to do with my later thinking about bacteria."

Lederberg entered the College of Physicians and Surgeons in 1944, while he was still in the U.S. Navy. Because of a space shortage at P & S, Ryan gave him a corner in the laboratory, where together they used a system of nutritional genetic markers to determine the role of DNA in the genetics of *Neurospora*. In 1945 Lederberg heard in one of his courses that because bacteria "exhibited no sexual behavior," little was known about

their genetic structure. He questioned this theory and immediately wrote down an outline for an experiment to determine recombination in bacteria, using the *Neurospora* genetic research method.

After two years at Columbia he took a leave of absence to accept a Jane Coffin Childs research fellowship, under which he went to work with Ryan's former mentor from Stanford, Edward Tatum, who had moved to Yale. There, says one historian of genetics, "Lederberg was handed undoubtedly the best Ph.D. problem in the history of biology on a silver—or rather Petri—plate." Tatum had brought from Stanford a strain of *E. coli* (colon bacillus) that responded to Lederberg's methodology. As his experiments "began working out," Lederberg extended his leave from P & S, but when the time came to make a final decision he chose to make research his career. In 1947, two days before receiving the Ph.D. from Yale, Joshua Lederberg officially registered as a graduate student. His Nobel prize was awarded—eleven years later—on the basis of his dissertation.

The discovery of the mechanism of genetic recombination in bacteria gave scientists not only new information on but also control over powerful new research tools. Bacteria are relatively simple to work with. They multiply rapidly and in small spaces. Much current genetic knowledge as well as the recently developed techniques for industrial applications derive from this early microbial work.

"Columbia doesn't get enough credit for its role in genetic research," says Lederberg. "The fact is that the work was started while I was still at Columbia. Almost the first experiment I did was the root of it. As an undergraduate I was doing graduate work. I had the right kind of discipline because I had Francis looking over my shoulder and guiding me. On the other hand, I was not a registered graduate student. I wasn't trying to fulfill a major in any subject. I don't think many zoology majors were taking the courses in chemistry, theoretical physics, logic, and mathematics that I was able to take.

"The research I got into was a very large gamble—the notion of seeing

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to working scientists. I could have stumbled badly even before
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whether a bacteria could be crossed using the genetic methodology. The typical graduate student would have great difficulty investing the year or so it might take to see whether it would work out. And if you're in the middle of a program, working toward a degree, you can't afford that. I was first an undergraduate, then a medical student doing research avocationally. I could afford to take risks other students couldn't. I wasn't aware of it at the time. This is all retrospective."

Lederberg joined the faculty of the College of Agriculture at the University of Wisconsin when he was twenty-two. "This looked like the best opportunity to do the research I was interested in. It took a few years before medical microbiologists woke up to what was happening in the genetics of microorganisms and to what its significance would be. So the first jobs were scattered." He recalls Wisconsin as a "very happy, nurturing setting." He produced a prodigious amount of research, particularly with geneticist Esther Zimmer Lederberg, his first wife. With student Norman Zinder, now a professor at Rockefeller University, he demonstrated the presence of DNA in bacteria. And he gained weight.

"He was enormous in those years," Elizabeth Ryan recalls. "Rabelaisian" was the word James Watson used in *The Double Helix* to describe "Joshua's nonstop three-to-five hour talks," his "godlike quality of each year expanding in size," and the "rabbinical complexity of his results."

In a group photo of twenty scientists taken at a 1949 Gene Conference on Shelter Island, Lederberg stands at one end next to Francis Ryan. Plump, in a striped jersey and slacks, Lederberg is the only man without a jacket, dress shirt, and tie. His is the youngest face. He holds his head down and to the side. His legs are slightly apart. His hands are behind his back. He is the stranger in the group. He has the look of someone's kid brother who has been told, "Come on, it's O.K."

In 1953 Lederberg was photographed at the Cold Spring Harbor Laboratories' Symposium at which Watson presented the prototype of the double helix. No longer a stranger, Lederberg stands in the

foreground, as large, round, and inscrutable as a Buddha.

Today, Lederberg is of medium build. His face is round, open, and gray-bearded. He sometimes works in shirt sleeves in his elegant wood-paneled office on Manhattan's East Side, which also boasts a fireplace and many, many book shelves. His wife, psychiatrist Dr. Marguerite Kirsch Lederberg, teases that it was for those shelves alone that he accepted the presidency of Rockefeller University.

Lederberg was still at Wisconsin in 1958 when he received a phone call in which he was told that he had won the Nobel prize. He thought the call was a practical joke. "I decided to lay low. It would have been very awkward to get congratulations and then have the whole thing be a bust," he remembers thinking.

He shared the prize and platform with Beadle and Tatum, Ryan's former colleagues, and felt his absent mentor as a presence. "If I could have foreseen the short time he had to live, I would have moved heaven and earth to be sure he could have been there in person," he says. Francis J. Ryan died in 1967 at the age of forty-six.

Lederberg says of the prizes, "The Nobel awards can't be allocated any better than they are now. It's got to be arbitrary at some point. And they don't choose too many incompetents as judges." As for receiving the prize at age thirty-three, he says, "It's not so appropriate for people quite so young. It would be just as well if there were a rule that you wait til age forty-five or fifty. I think I might have spent a few more years in a more focused way in the laboratory."

In 1959 Lederberg left Wisconsin to become a professor of genetics at Stanford University School of Medicine, where he remained for twenty years, also holding professorships in biology and computer science. "I am very much interested in trying to reconnect a lot of disciplines. I felt the reason bacterial genetics had taken so long to get started is that there were disciplines that never talked to one another."

While at Stanford, in a career that

moved him ever farther from the laboratory bench and closer to the administrative office—"the typical evolution of an academic," he calls it—he found time between 1966 and 1971 to write a weekly column for the *Washington Post* called "Science and Man."

Lederberg's commitment to the intercommunication of scientific disciplines touches on his role as president of Rockefeller University. Founded in 1901 by John D. Rockefeller as the Institute for Medical Research, it became a graduate university in 1954 and changed its name officially in 1965. It is devoted to research and training in the biological and biomedical sciences. "We're a nondepartmentalized institution," says Lederberg. "The labs are sort of free standing. We don't have people clustered in specific disciplines, talking only to one another. There's great encouragement for intercommunication." The challenge of understanding the wide range of research being done at the university and of stimulating interdisciplinary communication is, he says, one of the most exciting aspects of the presidency.

Lederberg calls New York "the world's largest scientific city." As might be expected when he enumerates the city's assets, he includes not only its universities, industrial laboratories, research institutions, and learned societies, but also the public library system. The city could be made "still more interesting as an academic center," he says, if even more communication could be established between campuses. It is not merely a matter of setting up meetings or seminars but of establishing "a deeper level of interaction, collaborative arrangements" that will bring "vitality and cross-fertilization." He mentions the possibility, for example, of selecting mathematicians who would divide their time between a "comprehensive department of mathematics," such as Columbia's, and "a community of biologists who do not really have a way to develop" such a department.

In addition to exchanges between scientists, Lederberg would like to see closer contact between active researchers and high school students. For all the in-

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Lederberg, *from page 35*

tellectual attainments of the mature Joshua Lederberg, it is the brash young reader of *Microbe Hunters* who powers these ideas. "I have in mind a way in which professors could adopt a few students. Courses are not enough. I'm saying, let them meet a Francis Ryan at an even earlier age than I did. High school students need to see, touch, and talk to working scientists. I could have stumbled badly even before I got to college. If there had been somebody I could have had half an hour with every three months to answer questions or tell me what to read—" he pauses, "those few minutes would have been very precious to me."

Even college students have trouble getting the guidance they need, Lederberg believes. The lack of interaction between faculty and students at urban universities is often ascribed—wrongly, in Lederberg's opinion—to inadequate on-campus housing. "I heard the same complaint at Stanford," he says. "There are different levels of barriers. It's a matter of students taking some time and initiative themselves, but they need encouragement. The brashest of them are also the shyest," he adds.

"Unless there's an organized program of counseling, it's not going to work." One of the programs at Stanford that Lederberg helped found and in which he participated was the development of a curriculum in biology for general education combined with a counseling program in which freshmen and sophomores met with juniors and seniors. "The students and counselors loved it," he says. "I can't remember anything having gone wrong. They knew what they were supposed to do, and when there were problems they knew where to go. It is working very well. But the reason is that there were a bunch of department chairmen willing to commit themselves to it on a voluntary basis."

Faced with the suggestion that he was giving students something of what Francis Ryan had given him, Joshua Lederberg answers, "Maybe so. Maybe so. But maybe I'm too impatient to do what Francis did. He had a degree of patience in dealing with me that I doubt I could have with anybody. But I've been conscious that I inherited a debt." □

Estelle Gilson is contributing editor of COLUMBIA. This is the third in her series of interviews with Nobel laureates.